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(71) Applicant: PHARMACIA S.P.A. [IT/IT]; Via Robert Koch, 1.2, I-20152 Milano (IT).

(72) Inventors: FANCELLI, Daniele; Via Gianella, 21, I-20152 Milano (IT). CACCIA, Carla; Via Torino, 31, I-21013 Gallarate (IT). SEVERINO, Dino; Via Magnasco Alessandro, 6, I-20100 Milano (IT). VAGHI, Fabrizio; Via Torino, 3, I-22079 Villa Guardia (IT). VARASI, Mario; Via Giambellino, 80, I-20146 Milano (IT).

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(57) Abstract

The present invention relates to the use of substituted dihydrobenzofuran derivatives having 5-HT_4 receptor agonist activity, which act as therapeutic prokinetic agents in treatment of gastrointestinal disorders such as, e.g., dyspepsia, gastro-oesophageal reflux disease (GORD) or gastroparesis. The compounds of the invention can also be useful in the treatment of CNS disorders, characterized by learning and/or memory dysfunctions. Several of these substituted dihydrobenzofuran derivatives are novel compounds and, as such, constitute a further object of the invention, together with the process for their preparation and the pharmaceutical compositions containing them.

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SUBSTITUTED DIHYDROBENZOFURAN DERIVATIVES AS 5-HT_4 AGONISTS

The present invention relates to the use of substituted dihydrobenzofuran derivatives which act as 5-HT_4 receptor agonists in the treatment of gastrointestinal disorders and CNS disorders, to certain novel compounds having 5-HT_4 receptor agonist activity, to a process for their preparation and to pharmaceutical compositions containing them.

A non classical 5-hydroxytriptamine receptor has been designed (Trends Pharmacol. Sci. (1992) 13, 141-5) as the 5-HT_4 receptor.

The prokinetic action of the substituted benzamide metoclopramide, which has long been in clinical use as a stimulant of gastrointestinal motility, is believed to be on the basis of its agonist effect on the 5-HT_4 receptor (Drug Design & Delivery (1988) 3, 273-295).

Some 5-HT_4 receptor agonists resulted active in appropriate animal behavioural tests for memory dysfunctions (Ghelardini et al. 19th C.I.N.P. Congress, Whashington, June 1994 ; Ghelardini et al. 10th European Society for Neurochemistry, Jerusalem, August 1994).

International patent application WO 93/16072 describes 5-

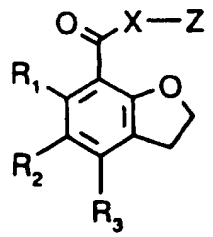
HT_4 receptor antagonists derived from the benzopyran, benzothiopyran or benzofuran nucleus.

International patent application WO 94/08995 relates to novel carboxylate or carboxamides of benzofuran or dibenzofuran having 5-HT_4 antagonist activity.

We have identified a class of substituted dihydrobenzofuran carboxylic acid derivatives which possess 5-HT_4 receptor agonist properties, despite their structural analogies with the closest prior art compounds such as, e.g., those disclosed in WO 93/16072 and WO 94/08995 having 5-HT_4 antagonist activity.

By virtue of their 5-HT_4 agonist activity, the compounds of the invention can be useful in all the pathologies wherein a stimulation of the 5-HT_4 receptors is needed and therefore, the compounds of the invention can be useful, for example, as therapeutic prokinetic agents in the treatment of gastrointestinal disorders such as, e.g., dyspepsia, gastro-oesophageal reflux disease (GORD) and gastroparesis, and/or also in the treatment of CNS disorders characterized by learning and/or memory dysfunctions.

Accordingly, the present invention relates to dihyrobenzofuran derivatives of formula (I)



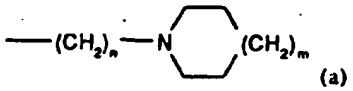
(I)

wherein

R_1, R_2 and R_3 are, each independently, hydrogen, C_1-C_6 alkyl, halogen, hydroxy, C_1-C_4 alkoxy, amino, C_1-C_4 alkylamino or C_1-C_4 di-alkylamino;

X is O, NH or CH_2;

Z is a group (a), (b), (c) or (d)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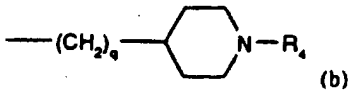
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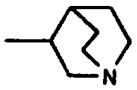
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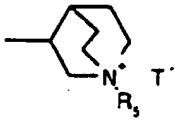

(d)

wherein

n is 1, 2, 3 or 4;

m is zero or 1;

q is zero, 1 or 2;

R_4 is hydrogen , C_1-C_6 alkyl, benzyl, cyclohexylmethyl or

$-CH_2-CH_2-SO_2NH-R_6$ in which R_6 is C_1-C_6 alkyl or benzyl;

R_5 is C_1-C_6 alkyl; and

T is halogen;

provided that, when Z is defined under (c), then X is O or CH_2, and their pharmaceutically acceptable salts, for use as 5-HT_4 agonists. The compounds of formula (I) can therefore be useful in the treatment of all the pathologies wherein a stimulation of the 5-HT_4 receptor is needed. As an example, the compounds of formula (I) may be useful as therapeutic prokinetic agents in the treatment of gastrointestinal disorders such as, for example, dyspepsia, gastro-oesophageal reflux disease (GORD) or gastroparesis. The compounds of formula (I) may also be useful, by virtue of their 5-HT_4 agonist properties, as cognition activators, in the treatment of CNS disorders characterized by learning and/or memory dysfunctions.

The alkyl, alkoxy and alkylamino groups may be branched or straight groups.

Representative examples of C_1-C_6 alkyl groups include methyl, ethyl, *n*- and *iso*-propyl, *n*-, *iso*-, *sec*- and tert-butyl.

Representative examples of C_1-C_4 alkoxy groups include methoxy and ethoxy.

A C_1-C_4 alkylamino group is, in particular, methylamino or ethylamino.

A C_1-C_4 di-alkylamino group is, in particular, dimethylamino or diethylamino.

Halogen includes fluorine, bromine, chlorine or iodine, in particular, chlorine or bromine.

The pharmaceutically acceptable salts of the compounds of formula (I) include acid addition salts with inorganic, e.g. hydrochloric, hydrobromic, sulphuric, and phosphoric acids, or organic, e.g. acetic, propionic, lactic, oxalic, malic, maleic, tartaric, citric, benzoic, mandelic, salicylic and fumaric acids.

Examples of pharmaceutically acceptable salts of the compounds of formula (I) wherein Z is a group (a) or (b) include quaternary derivatives such as, e.g., the compounds quaternised by compounds of formula R_x-W wherein R_x is C_1-C_6 alkyl or phenyl-C_1-C_6alkyl and W is a radical corresponding to an anion of an acid.

Preferably, R_x is C_1-C_4 alkyl or phenyl-C_1-C_4alkyl, in particular it is methyl, ethyl, *n*-propyl, *n*-butyl, benzyl or phenylethyl.

Preferably, W is a halide such as, e.g., chloride, bromide or iodide.

Examples of pharmaceutically acceptable salts of the compounds of formula (I) wherein Z is a group (a), (b) or (c) also include internal salts, such as, e.g. N-oxides.

The compounds of formula (I), their pharmaceutically

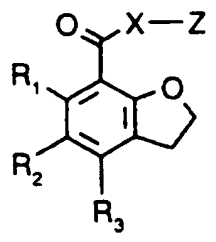
acceptable salts, (including quaternary derivatives and N-oxides) may also form pharmaceutically acceptable solvates, such as hydrates, which are also object of the present invention.

Compounds of formula (I) wherein Z is a group (c) contain an asymmetric carbon atom and, for this reason, they can exist either as a mixture of optical isomers (racemic mixture) or as a single optical isomers (enantiomers). The enantiomers can be separately synthesised from optically pure starting material or separated from the racemic mixture in a conventional manner.

The present invention also include within its scope both the metabolites and the pharmaceutically acceptable bio-precursors (otherwise known as pro-drugs) of the compounds of formula (I).

This invention also refers to a preferred class of compounds within formula (I), as novel compounds.

These compounds, which form a further object of the invention, are compounds of formula (I)



(I)

wherein

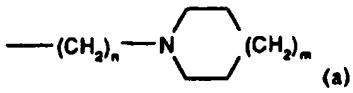
R_1 is hydrogen;

R_2 is chlorine or bromine;

R_3 is amino;

X is O or NH;

Z is a group (a), (b), (c) or (d):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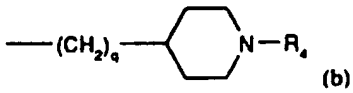
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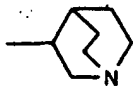
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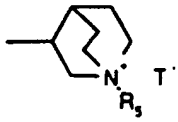

(d)

wherein

n is 2 or 3;

m is zero or 1;

q is 1 or 2;

R_4 is C_3-C_5 alkyl or $-CH_2-CH_2-SO_2NH-CH_3$;

R_5 is C_3-C_5 alkyl;and

T is chlorine or bromine;

provided that, when Z is defined under (c), then X is O;

and their pharmaceutically acceptable salts.

Examples of preferred compounds according to the invention are the following:

N-[1-butyl-1-azabicyclo[2,2,2]oct-3-yl]-4-amino-5-chloro-2,3-dihydrobenzo[b]furan-7-carboxamide bromide;

(1-azabicyclo[2,2,2]oct-3-yl)-4-amino-5-chloro-2,3-dihydrobenzo[b]furan-7-carboxylate;

(1-butyl-piperid-4-yl)methyl-4-amino-5-chloro-2,3-dihydrobenzo[b]furan-7-carboxylate;

(1-piperidyl)propyl-4-amino-5-chloro-2,3-dihydrobenzo[b]furan-7-carboxylate;

(1-piperidyl)ethyl-4-amino-5-chloro-2,3-dihydrobenzo[b]furan-7-carboxylate;

N-[(1-butyl-piperid-4-yl)methyl]-4-amino-5-chloro-2,3-dihydrobenzo[b]furan-7-carboxamide;

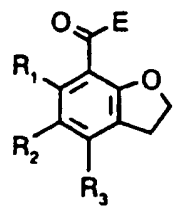
N-[(1-piperidyl)propyl]-4-amino-5-chloro-2,3-dihydrobenzo[b] furan-7-carboxamide; and

N-[(1-piperidyl)ethyl]-4-amino-5-chloro-2,3-dihydrobenzo[b]furan-7-carboxamide;

if the case either as a single isomer or as a mixture of isomers thereof, and the pharmaceutically acceptable salts thereof.

The compounds of formula (I) can be obtained by a process comprising:

A) reacting a compound of formula (II)



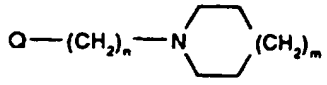
(II)

wherein

E is OH, Cl, Br or 1-imidazolyl, and

R_1, R_2 and R_3 are, each independently, hydrogen, C_1-C_6 alkyl, halogen, hydroxy, C_1-C_4 alkoxy, amino, C_1-C_4 alkylamino or C_1-C_4 di-alkylamino,

with an amine or an alcohol of formula (III), (IV) or (V)



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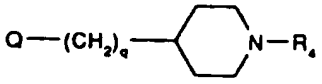

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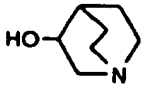


(V)

wherein

Q is OH or NH_2;

n is 1,2,3 or 4;

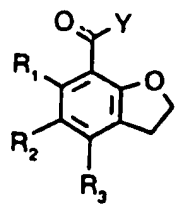
m is 0 or 1;

q is 0,1 or 2; and

R_4 is hydrogen, C_1-C_6 alkyl, benzyl, cyclohexylmethyl or $-CH_2-CH_2-SO_2-NH-R_6$ in which R_6 is C_1-C_6 alkyl or benzyl

so obtaining a compound of formula (I) wherein R_1, R_2, R_3 and R_6 are as defined above, X is NH or O and Z is a group (a), (b) or (c); or

B) reacting a compound of formula (VI)



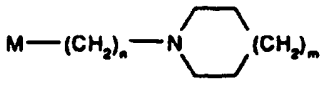
(VI)

wherein

Y is OH, Cl, Br or CH_3-NH-OCH_3, and

R_1, R_2 and R_3 are are as defined above,

with an organometallic derivative of formula (VII), (VIII) or (IX)



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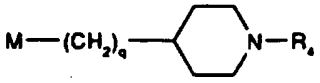
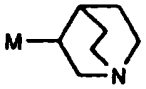


(VIII)



(IX)

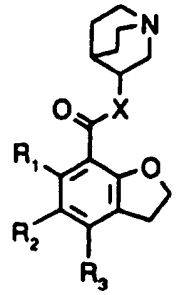
wherein

M is MgBr, MgCl or Li, and

n, m, q, R_4 and R_5 are as defined above,

so obtaining a compound of formula (I) wherein R_1, R_2 and R_3 are as defined above, X is CH_2 and Z is a group (a), (b) or (c); or

C) reacting a compound of formula (X)



(X)

wherein R_1, R_2, R_3 and X are as defined above, and

X is NH, O or CH_2,

with an alkyl halide of formula R_5T wherein R_5 is C_1-C_6 alkyl and T is halogen, so obtaining a compound of formula (I) wherein R_1, R_2, R_3 are as defined above, X is O, NH, or CH_2 and Z is a group (d) ; and, if desired, when a compound of formula (I) contains an asymmetric carbon atom,

D) resolving the racemic mixture of a compound of formula (I) into the single isomers; and/or, if desired,

E) converting a compound of formula (I) into a pharmaceutically acceptable salt thereof.

The reaction of a compound of formula (II) with a compound of formula (III), (IV) or (V) under step A) is an analogy process and can be carried out according to well known methods in the art. For instance, an acyl halide of formula (II) can be reacted with an alcohol or an amine of formula (III), (IV) or (V) in a suitable organic solvent such as, for instance, dichloromethane, tetrahydrofurane or acetonitrile, at a temperature ranging from about 0°C to about the reflux temperature of the mixture, in the presence of a proton scavenger such as, for instance, triethylamine, sodium hydrogen carbonate or potassium carbonate.

The reaction of a compound of formula (VI) with a compound of formula (VII), (VIII) or (IX) under step B) can also be carried out according to well known methods in the art. For instance, an acyl halide of formula (VI) can be reacted

with a Grignard reactive of formula (VII), (VIII) or (IX) in a suitable organic solvent such as, e.g., tetrahydrofuran or diethyl ether in the presence of, e.g., Fe(acetylacetonate)$_3$ or CuI, at a temperature ranging from about -78°C to about 30°C.

The reaction of a compound of formula (X) with an alkyl halide R_5T under step C) can be carried out according to standard methodologies. For instance, a compound of formula (X) can be reacted with a compound R_5T as defined above, in the presence of a suitable organic solvent such as, e.g., methanol or ethanol, at a temperature ranging from about 30°C to about the reflux temperature of the mixture.

The carboxylic acids of formulae (II) and (VI) wherein E and Y are OH are either commercially available or known products.

The acid derivatives (II) and (VI) are either known products (EP 0 234 872 A1 Adria Laboratories Inc.) or may be prepared from the corresponding acids by methods well known in the art.

The alcohols and amines of formulae (III), (IV) and (V) are either commercially available or known products.

The organometallic derivatives of formulae (VII), (VIII) and (IX) can be prepared by standard methodologies from the corresponding alkyl halides which are either commercially available products or can be easily prepared from the

corresponding alcohols of formulae (III), (IV) and (V). The compounds of formula (X) wherein X is NH are known compounds (EP 0 234 872 A1 Adria Laboratories Inc.).

The alkyl halides of formula R_5T are commercially available products.

The separation of a mixture of isomers of a compound of the invention into single isomers and the conversion of a compound of formula (I) into a pharmaceutically acceptable salt thereof can be carried out according to well known methods in the art.

As already said, the compounds of the present invention are potent agonists of 5-HT (serotonin) on 5-HT_4 receptors and can therefore be used in the treatment of the pathologies wherein a stimulation of the 5-HT_4 receptor is needed. In particular, as 5-HT_4 agonists are known being stimulant of gastrointestinal motility, the compounds of the present invention can be useful as therapeutic prokinetic agents, for example, in the treatment of gastrointestinal disease such as, for instance, dyspepsia, gastro-oesophageal reflux disease (GORD) or gastroparesis. In addition, in view of the fact that 5-HT_4 receptors are believed to be involved in synaptic plasticity events and in memory processes (CNS Drugs (1994) 1, 6-15), and that it has been demonstrated that 5-HT_4 receptor stimulation facilitates in vivo acetylcholine release in rat frontal cortex (NeuroReport

(1994) 5, 1230-2), another application of the compounds of the invention may also be as cognition activators in the treatment of CNS disorders characterized by learning and/or memory dysfunctions.

5-HT_4 receptor affinity of the compounds of the present invention was determined by the inhibition of the binding of the 5-HT_4 receptor radioligand [^{3}H]-GR-113808 in rat striatum, according to the method of Grossman et al. (Br.J.Pharmacol., 1993, 109,618-624).

The activity of the compounds of the present invention as 5-HT_4 agonists was evaluated "in vitro" by the receptor-mediated relaxation responses of rat, carbachol precontracted oesophageal muscolaris mucosae, following the method of Baxter et al., (Naunhyn Schmiedeberg's Arch. Pharmacol., 1991, 343, 439-446).

As an example, a representative group of compounds according to this invention, namely

(S)-(+)-N-[1-butyl-1-azabicyclo[2,2,2]oct-3-yl]-4-amino-5-chloro-2,3-dihydrobenzo[b]furan-7-carboxamide bromide monohydrate (internal code FCE 28773A);

(1-butyl-piperid-4-yl)methyl-4-amino-5-chloro-2,3-dihydrobenzo[b]furan-7-carboxylate hydrochloride (internal code FCE 29029A);

N-[(1-butyl-piperid-4-yl)methyl]-4-amino-5-chloro-2,3-dihydrobenzo[b]furan-7-carboxamide hydrochloride

(internal code FCE 29030A);

(1-piperidyl)ethyl-4-amino-5-chloro-2,3-dihydrobenzo[b] furan-7-carboxylate hydrochloride hemihydrate (internal code FCE 29032A);

N-[(1-piperidyl)ethyl]-4-amino-5-chloro-2,3-dihydrobenzo [b]furan-7-carboxamide hydrochloride hydrate (internal code FCE 29033A);

(1-piperidyl)propyl-4-amino-5-chloro-2,3-dihydrobenzo[b]furan-7-carboxylate hydrochloride hemihydrate (internal code FCE 29031A);

N-[(1-piperidyl)propyl]-4-amino-5-chloro-2,3-dihydrobenzo[b]furan-7-carboxamide hydrochloride hydrate (internal code FCE 29034A) and

(S)-(+)-(1-azabicyclo[2,2,2]oct-3-yl)-4-amino-5-chloro-2,3-dihydrobenzo[b]furan-7-carboxylate hydrochloride (internal code FCE 28797A);

were tested according to the methods described above and the obtained results are reported on Table 1.

Table 1

Compound	Binding assay K_i (nM)	5-HT_4R activity EC_{50} (nM)
FCE 28773A	1.9	8.5 (i.a.=0.52)
FCE 29029A	0.13	5.67 (i.a.=1.0)
FCE 29030A	1.9	4.49 (i.a.=0.59)

FCE 29032A	0.94	2.02 (i.a.=0.71)
FCE 29033A	41	35.4 (i.a.=0.65)
FCE 29031A	4.5	7.43 (i.a.=0.70)
FCE 29034A	9.6	19.3 (i.a.=0.60)
FCE 28797A	8.3	11.1 (i.a.=0.71)

$$K_i = \frac{IC_{50}}{1 + \frac{[L]}{Kd}}$$

where

IC_{50} = concentration of the tested compound which forces the displacements of 50% of the bound radioligand concentration, obtained in the absence of inhibitor.

[L] = radioligand concentration

Kd = dissociation constant of the radioligand-receptor complex.

EC_{50} = efficacy concentration: concentration of the tested compound which induces 50% of the max. response (in this case 50% of the max. relaxation).

i.a. = intrinsic activity: max. response/max response of the natural agonist (in this case max. relaxation/5-HT max.relaxation).

The tabulated results clearly show that the compounds of the invention exhibit high affinity for the 5-HT_4 receptor sites and, in the same time, are particularly effective in

promoting 5-HT_4 receptor activity.

The compounds of the invention can be administered in a variety of dosage forms, e.g. orally, in the form of tablets, capsules, sugar or film coated tablets, liquid solutions or suspensions; rectally in the form of suppositories; parenterally, e.g. intramuscolarly, or by intravenous injection or infusion.

The dosage depends on the age, weight, conditions of the patient and on the administration route; for example, the dosage adopted for oral administration to adult humans e.g. for the representative compound of the invention FCE 29034A may range from about 1 to about 500 mg pro dose, from 1 to 5 times daily.

The invention includes pharmaceutical compositions comprising a compound of the invention as an active principle in association with a pharmaceutically acceptable excipient (which can be a carrier or a diluent).

The pharmaceutical compositions containing the compounds of the invention are usually prepared following conventional methods and are administered in a pharmaceutically suitable form.

For example, the solid oral forms may contain, together with the active compound, diluents, e.g. lactose, destrose, saccharose, cellulose, corn starch or potato starch; lubricants, e.g. silica, talc, stearic acid, magnesium or

calcium stearate, and/or polyethylene glycols; binding agents, e.g. starches, arabic gums, gelatin, methylcellulose, carboxymethylcellulose or polyvinyl pyrrolidone; disaggregating agents, e.g. a starch, alginic acid, alginates or sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents such as lecithin, polysorbates, laurylsulphates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. Said pharmaceutical preparations may be manufactured in known manner, for example, by means of mixing, granulating, tabletting, sugar-coating, or film-coating processes.

The liquid dispersion for oral administration may be e.g. syrups, emulsions and suspension.

The syrups may contain as carrier, for example, saccharose or saccharose with glycerine and/or mannitol and/or sorbitol.

The suspensions and the emulsions may contain as carrier, for example, a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol.

The suspensions or solutions for intramuscolar injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol,

and, if desidered, a suitable amount of lidocaine hydrochloride. The solutions for intravenous injections or infusion may contain as carrier, for example, sterile water or preferably they may be in the form of sterile, acqueous, isotonic saline solutions.

The suppositories may contain together with the active compound a pharmaceutically acceptable carrier, e.g. cocoa butter, polyethylene glycol, a polyoxyethylene sorbitan fatty acid ester surfactant or lecithin.

The following examples illustrate but do not limit the invention.

Example 1

A mixture of 4-amino-5-chloro-2,3-dihydrobenzo[b]furan-7-carboxylic acid (0.700g , 3.28 mmol) and carbonyldiimidazol (0.580g , 3.60 mmol) in 10 ml of anhydrous tetrahydrofuran was heated at 40°C for 1.5h. Afterward (1-piperidyl)ethylamine (0.427ml , 4.92mmol) in 5ml of tetrahydrofuran was added, the mixture was heated for additional 2h and stirred at 22°C for 16h. Volatilies were evaporated under reduced pressure and the residue was taken up with water and ethyl acetate; the layers were separated, the organic layer was dried over anhydrous sodium sulphate and evaporated to give 1.0 of raw material, which was partially purified by column chromatography over silica gel

(eluant chloroform/methyl alcohol/ammonia solution 30% 46:4:0.1). The carboxamide was conveniently isolated as its hydrochloride by adding to the free base in aceton/isopropyl alcohol 1 equivalent of hydrochloric acid in isopropyl alcohol. Precipitated solid was filtered, washed with diethyl ether and dried, yielding 746mg (60%) of N-[(1-piperidyl)ethyl]-4-amino-5-chloro-2,3-dihydrobenzo[b]furan-7-carboxamide hydrochloride hydrate as a colorless solid (m.p. = 237-239°C).

Analogously, the following compounds were prepared :

N-[(1-piperidyl)propyl]-4-amino-5-chloro-2,3-dihydrobenzo[b]furan-7-carboxamide hydrochloride hydrate (m.p. 192-194°C); and

N-[(1-butyl-piperid-4-yl)methyl]-4-amino-5-chloro-2,3-dihydrobenzo[b]furan-7-carboxamide hydrochloride (m.p.260-262°C).

Example 2

A mixture of 4-amino-5-chloro-2,3-dihydrobenzo[b]furan-7-carboxylic acid (1.61g , 7.56 mmol) and carbonyldiimidazol (1.35g , 8.32 mmol) in 15 ml of anhydrous tetrahydrofuran was heated at 40°C for 1.5h. Afterward a solution of N-(1-butyl-piperid-4-yl)methyl alcohol (2.59g , 15.1mmol) and 1,8-diazabicyclo[5,4,0]undec-7-en (DBU) (1.13ml , 7.56 mmol) in 10ml of tetrahydrofuran was added and the mixture was heated for additional 2.5h. Volatilies were evaporated

under reduced pressure and the residue was taken up with water and diethyl ether; the layers were separated, the organic layer was dried over anhydrous sodium sulphate and evaporated to give 3.5g of raw material, which was purified by column chromatography over silica gel (eluant chloroform/methyl alcohol 46:4) yielding 1.5g (54%) of (1-butyl-piperid-4-yl)methyl-4-amino-5-chloro-2,3-dihydrobenzo[b]furan-7-carboxylate (m.p. = 124-126°C) as a colorless solid.

Analogously, the following compounds can be prepared :

(1-piperidyl)ethyl-4-amino-5-chloro-2,3-dihydrobenzo[b]furan-7-carboxylate (m.p. = 152-154°C);

(1-piperidyl)propyl-4-amino-5-chloro-2,3-dihydrobenzo[b]furan-7-carboxylate; and

(S)-(+)-(1-azabicyclo[2,2,2]oct-3-yl)-4-amino-5-chloro-2,3-dihydrobenzo[b]furan-7-carboxylate.

Example 3

1 equivalent of hydrochloric acid in isopropyl alcohol was added at 5°C to a stirred solution of (1-piperidyl)propyl 4-amino-5-chloro-2,3-dihydrobenzo[b]furan-7-carboxylate (337mg , 0.996mmol) in aceton . Precipitated solid was was filtered, washed with diethyl ether and dried, yielding 342mg (89%) of (1-piperidyl)propyl 4-amino-5-chloro-2,3-dihydrobenzo[b]furan-7-carboxylate hydrochloride hemihydrate as a colorless solid (m.p. = 226-228°C).

Analogously, the following compounds were prepared : (1-piperidyl)ethyl-4-amino-5-chloro-2,3-dihydrobenzo[b]furan-7-carboxylate hydrochloride hemihydrate (m.p. 255-257°C);

(1-butyl-piperid-4-yl)methyl-4-amino-5-chloro-2,3-dihydrobenzo[b]furan-7-carboxylate hydrochloride (m.p. = 238-240°C); and

(S)-(+)-(1-azabicyclo[2,2,2]oct-3-yl)-4-amino-5-chloro-2,3-dihydrobenzo[b]furan-7-carboxylate hydrochloride (m.p. 283.5-284.5); $[\alpha]_D^{23}$ = +82 (c = 0.94 , DMF).

Example 4

A mixture of (S)-(+)-[1-azabicyclo[2,2,2]oct-3-yl]-4-amino-5-chloro-2,3-dihydrobenzo[b]furan-7-carboxamide (0.508g , 1.58mmol) and n-butylbromide (0.169ml , 1.58mmol) in ethyl alcohol was heated under reflux for 16h. The solvent was removed under reduced pressure, the residue was purified by column chromatography over silica gel (eluent chloroform/ methyl alcohol 4:1) and crystallized by water giving 0.43g (60%) of (S)-(+)-N-[1-butyl-1-azabicyclo[2,2,2]oct-3-yl]-4-amino-5-chloro-2,3-dihydrobenzo[b]furan-7-carboxamide bromide monohydrate as an amorphous colorless solid ; $[\alpha]_D^{23}$ = +36 (c = 0.94 , DMF).

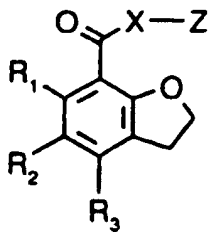
Example 5

With the usual methods of pharmaceutical technique, preparation can be made of capsules having the following composition:

N-(1-piperidyl)ethyl-4-amino-5-chloro-2,3-dihydrobenzo[b]furan-7-carboxamide hydrochloride hydrate	50mg
talc	2mg
starch	2mg
microcristalline cellulose	6mg
magnesium stearate	1mg

CLAIMS

1. A dihydrobenzofuran derivative of formula (I)



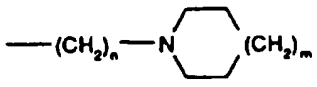
(I)

wherein

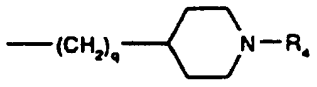
R_1, R_2 and R_3 are, each independently, hydrogen, C_1-C_6 alkyl, halogen, hydroxy, C_1-C_4 alkoxy, amino, C_1-C_4 alkylamino or C_1-C_4 di-alkylamino;

X is O, NH or CH_2;

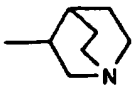
Z is a group (a), (b), (c) or (d)



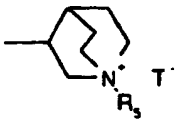
(a)



(b)



(c)



(d)

wherein

n is 1, 2, 3 or 4;

m is zero or 1;

q is zero, 1 or 2;

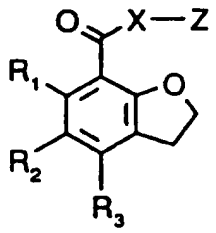
R_4 is hydrogen , C_1-C_6 alkyl, benzyl, cyclohexylmethyl or $-CH_2-CH_2-SO_2NH-R_6$ in which R_6 is C_1-C_6 alkyl or benzyl;

R_5 is C_1-C_6 alkyl; and

T is halogen;

provided that, when Z is defined under (c), then X is O or CH_2; or a pharmaceutically acceptable salt thereof, for use as a 5-HT_4 receptor agonist.

2. A dihydrobenzofuran derivative of formula (I):



(I)

wherein

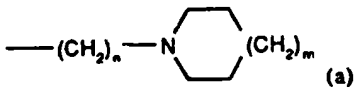
R_1 is hydrogen;

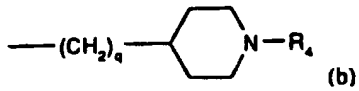
R_2 is chlorine or bromine;

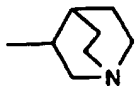
R_3 is amino;

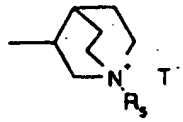
X is O or NH;

Z is a group (a), (b), (c) or (d)


(a)


(b)


(c)


(d)

wherein

n is 2 or 3;

m is zero or 1;

q is 1 or 2;

R_4 is C_3-C_5 alkyl or $-CH_2-CH_2-SO_2NH-CH_3$;

R_5 is C_3-C_5 alkyl; and

T is chlorine or bromine;

provided that, when Z is defined under (c), then X is O;

or a pharmaceutically acceptable salt thereof.

3. A compound as claimed in claim 2, selected from:

N-[1-butyl-1-azabicyclo[2,2,2]oct-3-yl]-4-amino-5-chloro-2,3-dihydrobenzo[b]furan-7-carboxamide bromide;

(1-azabicyclo[2,2,2]oct-3-yl)-4-amino-5-chloro-2,3-dihydrobenzo[b]furan-7-carboxylate;

(1-butyl-piperid-4-yl)methyl-4-amino-5-chloro-2,3-dihydrobenzo[b]furan-7-carboxylate;

(1-piperidyl)propyl-4-amino-5-chloro-2,3-dihydrobenzo

[b]furan-7-carboxylate;

(1-piperidyl)ethyl-4-amino-5-chloro-2,3-dihydrobenzo [b]furan-7-carboxylate;

N-[(1-butyl-piperid-4-yl)methyl]-4-amino-5-chloro-2,3-dihydrobenzo[b]furan-7-carboxamide;

N-[(1-piperidyl)propyl] 4-amino-5-chloro-2,3-dihydrobenzo[b]furan-7-carboxamide; and

N-[(1-piperidyl)ethyl]-4-amino-5-chloro-2,3-dihydrobenzo[b]furan-7-carboxamide;

if the case either as a single isomer or as a mixture of isomers, and the pharmaceutically acceptable salts thereof.

4. A compound as claimed in claim 2 or 3 for use as a $5HT_4$ receptor agonist.

5. A compound as claimed in claim 1,2 OR 3 for use as a $5\text{-}HT_4$ receptor agonist in the treatment of a pathology wherein stimulation of a $5\text{-}HT_4$ receptor is needed.

6. A compound as claimed in claim 1, 2 or 3 for use as a therapeutic prokinetic agent in the treatment of gastrointestinal disorders.

7. A compound as claimed in claim 6 wherein the

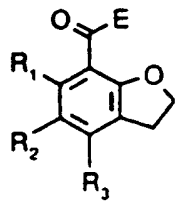
gastrointestinal disorder is dyspepsia, gastro-oesophageal reflux disease (GORD) or gastroparesis.

8. A compound as claimed in claim 1, 2 or 3 for use as a cognition activator in the treatment of CNS disorders characterized by learning and/or memory dysfunctions.

9. Use of a compound as defined in claim 1, 2, or 3 in the preparation of a medicament for use as a $5HT_4$ receptor agonist.

10. A process for preparing a dihydrobenzofuran derivative of formula (I) as defined in claim 1 or 2, or a pharmaceutically acceptable salt thereof, said process comprising:

A) reacting of a compound of formula (II)



(II)

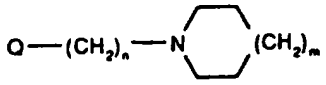
wherein

E is OH, Cl, Br or 1-imidazolyl, and

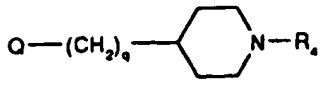
R_1, R_2 and R_3 are, each independently, hydrogen, C_1-C_6 alkyl, halogen, hydroxy, C_1-C_4 alkoxy, amino,

C_1-C_4 alkylamino or C_1-C_4 di-alkylamino,

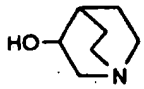
with an amine or an alcohol of formula (III), (IV) or (V)



(III)



(IV)



(V)

wherein

Q is OH or NH_2;

n is 1,2,3 or 4;

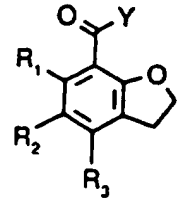
m is 0 or 1;

q is 0,1 or 2; and

R_4 is hydrogen, C_1-C_6 alkyl, benzyl, cyclohexylmethyl or $-CH_2-CH_2-SO_2NH-R_6$ in which R_6 is C_1-C_6 alkyl or benzyl,

so obtaining a compound of formula (I) wherein R_1, R_2, R_3 and R_6 are as defined above, X is NH or O and Z is a group (a), (b) or (c); or

B) reacting a compound of formula (VI)



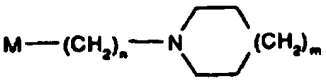
(VI)

wherein

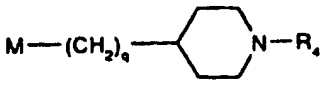
Y is OH, Cl, Br or $CH_3-NH-OCH_3$, and

R_1, R_2 and R_3 are are as defined above,

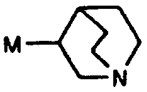
with an organometallic derivative of formula (VII), (VIII) or (IX)



(VII)



(VIII)



(IX)

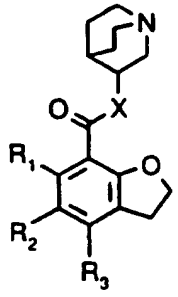
wherein

M is MgBr, MgCl or Li, and

n, m, q, R_4 and R_5 are as defined above,

so obtaining a compound of formula (I) wherein R_1, R_2 and R_3 are as defined above, X is CH_2 and Z is a group (a), (b) or (c); or

C) reacting a compound of formula (X)



(X)

wherein

R_1, R_2, R_3 and X are as defined above, and

X is NH, O or CH_2,

with an alkyl halide of formula R_5T wherein R_5 is

C_1-C_6 alkyl and T is halogen, so obtaining a compound of formula (I) wherein R_1, R_2, and R_3 are as defined above, X is O, NH or CH_2 and Z is a group (d); and, if desired, when a compound of formula (I) contains an asymmetric carbon atom,

D) resolving the racemic mixture of a compound of formula (I) into the single isomers; and/or, if desired,

E) converting a compound of formula (I) into a pharmaceutically acceptable salt thereof.

11. A pharmaceutical composition comprising a carrier and/or a pharmaceutically acceptable diluent and, as an active substance, a compound as defined in claim 1, 2 or 3.

12. A pharmaceutical composition according to claim 11, for use in the treatment of a pathology wherein stimulation of a $5HT_4$ receptor is needed.

13. A pharmaceutical composition according to claim 11, for use as a therapeutic prokinetic agent in the treatment of gastrointestinal disorders.

14. A pharmaceutical composition according to claim 13 wherein the gastrointestinal disorder is dyspepsia,

gastro-oesophageal reflux disease (GORD) or gastroparesis.

15. A pharmaceutical composition according to claim 11 for use as a cognition activator in the treatment of CNS disorders characterized by learning and/or memory dysfunctions.

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/EP 96/01482

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D307/79 C07D405/12 A61K31/445 C07D453/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	BIOORG. MED. CHEM. LETT. (BMCLE8,0960894X);96; VOL.6 (3); PP.263-6, PHARM. & UPJOHN;CNS PRECLIN. R&D; NERVIANO; 20014; ITALY (IT), XP002007988 FANCELLI D ET AL: "Serotoninergic 5-HT3 and 5-HT4 receptor activities of dihydrobenzofuran carboxylic acid derivatives" see the whole document --- -/--	1-15

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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Date of the actual completion of the international search	Date of mailing of the international search report
22 July 1996	14.08.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Scruton-Evans, I

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Internal Application No
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